Corticosteroids for Managing Pediatric Sepsis and Septic Shock

A Systematic Review and Meta-analysis

Jiawen Deng, BHSc,† Nefissa Bedri, BHSc,‡ Qi Kang Zuo, BSc,§ Maryam Azab, BSc,*† Oswin Chang, BHSc,§ Riya Virdi,§ Jay Hung, BHSc,¶ Kaden Venugopal, BHSc, MSc(c),‡ Umair Tahir, BHSc,* and Kiyan Heybati, BHSc, MSc‖*

Objective: To assess the efficacy and safety of corticosteroids for the management of pediatric sepsis and septic shock.

Data Sources: Ovid MEDLINE, Ovid Embase, CENTRAL, Web of Science (Core Collection) and China National Knowledge Infrastructure were systematically searched up to September 2023. Preprint servers, clinical trial registries and the reference sections of previous reviews were hand-searched.

Study Selection: Randomized controlled trials that enrolled pediatric sepsis, septic shock or systemic inflammatory response syndrome patients, compared the use of corticosteroid regimens against standard sepsis care and reported eligible outcomes were included. Title/abstract and full-text screening were conducted in-duplicate.

Data Extraction: Eligible articles were extracted using a standardized form in-duplicate. Outcomes extracted include mortality incidence, hospital and pediatric intensive care unit length of stay, duration of shock, incidence of adverse events and serious adverse events and incidence of corticosteroid-related adverse events. The risk of bias was assessed using the Revised Cochrane Risk of Bias Tool for Assessing Randomized Trials.

Data Synthesis: Random-effects meta-analyses were conducted, and the quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations approach. Sixteen randomized controlled trials (N = 973) were included. Corticosteroid use may be associated with reduced mortality risks (risk ratio: 0.65, 95% CI: 0.50–0.85), shorter length of hospital stay (MD: −3.76 days, 95% CI: −6.66 to −0.86), and shorter pediatric intensive care unit length of stay (MD −2.34 days, 95% CI: −3.14 to −1.53 days). Corticosteroid use may be associated with gastrointestinal bleeding but not a higher risk of secondary infection. No studies reported on serious adverse events. All findings were based on low to very low quality of evidence.

Conclusions: While corticosteroids show promise for managing pediatric sepsis and septic shock, the question of how to select the best candidate and the most optimal regimen remains unanswered. Future trials need to focus on assessing corticosteroid-related adverse events and stratifying patient inclusion by sepsis subphenotypes.

Key Words: sepsis, septic shock, corticosteroid, systematic review, meta-analysis

(*Pediatr Infect Dis J* 2024;XX:00–00)

Pediatric sepsis is a critical and potentially life-threatening condition characterized by dysregulated and amplified immune responses to infections.[1] Without immediate interventions, pediatric sepsis can escalate into septic shock, causing significant hemodynamic instability that increases the likelihood of mortality.[2] Severe sepsis and septic shock remain a leading cause of childhood morbidity and mortality around the world, with 25 million incident cases reported by the Global Burden of Disease study in 2017.[3] Once diagnosed, the case fatality rate of these conditions is estimated to be around 25%.[4]

Given the pathophysiology of sepsis, corticosteroids have been proposed as a biologically plausible therapy due to their immunomodulatory and vasoconstrictive properties. However, landmark randomized controlled trials (RCTs) assessing corticosteroids are restricted to adult patients and report conflicting results in corticosteroids' efficacy for reducing sepsis-associated deterioration.[5,6] While the latest Surviving Sepsis Campaign guidelines suggested that IV hydrocortisone may be considered in hemodynamically unstable pediatric patients refractory to fluid resuscitation and vasoconstrictors, this recommendation was based primarily on observational evidence. The guideline also states that "no high-quality investigations currently support or refute the routine use of adjunctive corticosteroids for pediatric septic shock or other sepsis-associated organ dysfunction.[1]"

Evidently, there is a need to identify and summarize RCT data to provide better support for or against the use of corticosteroids in pediatric patients with sepsis and septic shock. A previous meta-analysis on the subject was published by Menon et al[7] in 2013, which did not find an association between corticosteroid use and reduced mortality in this population.[7] The current investigation aims to provide an updated systematic review that incorporates data from several recently published RCTs, as well as to provide additional assessments regarding the safety profile of corticosteroids in pediatric patients with sepsis and septic shock.

Accepted for publication August 14, 2024

From the *Temerty Faculty of Medicine, University of Toronto, Toronto, ON; †Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON; ‡Faculty of Health Sciences, University of Ottawa, Ottawa, ON; §Faculty of Medicine, University of British Columbia, Vancouver, BC; ¶Faculty of Health Sciences, Queen's University, Kingston, ON; and ‖Mayo Clinic Alix School of Medicine (Jacksonville), Mayo Clinic, Jacksonville, FL.

The authors have no funding or conflicts of interest to disclose.

Preliminary results from this review were presented at the 2024 American Thoracic Society (ATS) International Conference in San Diego, California.

All available data is disclosed in the manuscript, its accompanying figures/tables, and supplementary materials.

J.D.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, visualization, writing—original draft, writing—review and editing. N.B.: investigation, writing—original draft, writing—review and editing. Q.K.Z.: data curation, investigation, project administration, supervision, investigation, writing—original draft, writing—review and editing. M.A., O.C., R.V., J.H., K.V., and U.T.: investigation, writing—review and editing. K.H.: conceptualization, investigation, project administration, resources, supervision, writing—original draft, writing—review and editing. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

Address for correspondence: Jiawen Deng, BHSc, Temerty Faculty of Medicine, University of Toronto, 1 King's College Cir, Toronto, ON M5S 1A8, Canada. E-mail: dengj35@mcmaster.ca.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0891-3668/24/XXXX-0000
DOI: 10.1097/INF.0000000000004551

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

SHOUT
SHARE
IT

METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[8] (Table, Supplemental Digital Content 1, http://links.lww.com/INF/F725). This review was prospectively registered on PROSPERO (CRD42023487819).

Study Identification

A database search was conducted in Ovid MEDLINE, Ovid Embase, CENTRAL, Web of Science (Core Collection), and China National Knowledge Infrastructure from inception to September 3rd, 2023 for relevant RCTs. The search strategy was piloted on MEDLINE using relevant MeSH terms and title/abstract headings such as "sepsis," "bacteremia," "steroid" and "hydrocortisone," as well as a modified version of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE.[9] The search strategy was then translated to other databases using database-specific keywords. The search strategies used are tabulated in Tables, Supplemental Digital Content 2–6, http://links.lww.com/INF/F726. We did not apply any language or date restrictions.

In addition to the database searches, we conducted a handsearch for relevant preprints on medRxiv and Research Square, relevant clinical trial registrations on ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, as well as relevant references from prior systematic reviews.[7,10]

Eligibility Criteria and Outcome Measures

Publications reporting data from RCTs were included if they met the following eligibility criteria: (1) enrolled pediatric patients under 18 years of age and diagnosed with sepsis, septic shock or systemic inflammatory response syndrome with a suspected infectious source; (2) compared the use of corticosteroid therapy against standard sepsis care, or against standard sepsis care with a placebo; and (3) reported any outcomes of interest.

Our efficacy outcomes included: (1) incidence of mortality, (2) hospital length of stay, (3) pediatric intensive care unit (PICU) length of stay, and (4) duration of shock. Our safety outcomes included: (1) incidence of adverse events, (2) incidence of serious adverse events, and (3) incidence of corticosteroid-related adverse events (ie, gastrointestinal bleeding, secondary infections, hyperglycemia and hypernatremia).

Study Selection and Data Extraction

Pairs of reviewers assessed the retrieved titles/abstracts for eligibility independently and in-duplicate. Records deemed eligible were then entered into an in-duplicate full-text screening process. Both screening steps were facilitated by Covidence (https://www.covidence.org/), and disagreements were resolved through consensus with senior authors.

Data extraction was performed in-duplicate using standardized extraction forms with the following fields: (1) study metadata (author names, publication year, trial registry number and study settings), (2) study methodology (inclusion and exclusion criteria, study duration, randomization and allocation concealment methods, blinding methods and treatment descriptions), (3) baseline patient characteristics (number of patients randomized and analyzed, sex distribution and mean/median age with variance measures) and (4) outcome data. Disagreements during data extraction were resolved via discussions or by recruiting a third author to review the data. We preferentially extracted data from intention-to-treat or modified intention-to-treat analyses.

In cases of unclear or missing data, we attempted to contact the corresponding authors for unpublished information. Details of contacts for missing data are tabulated in Table, Supplemental Digital Content 7, http://links.lww.com/INF/F727. For studies reporting nonparametric values for continuous outcome data (eg, medians with interquartile range), we assessed data normality using methods proposed by Shi et al[11] and performed an imputation of the mean and standard deviation[12–14] only if the data were not deemed as skewed. Skewed results were presented narratively.

Risk of Bias Assessment

The risk of bias was assessed in-duplicate for each study using the Revised Cochrane Risk of Bias Tool for Assessing Randomized Trials (RoB2).[15] Disagreements in the RoB2 ratings were resolved through consensus.

Statistical Analysis

Extracted outcome data were pooled in random-effects meta-analyses using the meta package in *R* and visualized as forest plots. The relative treatment effect and associated variances were expressed as risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs). We applied treatment-arm continuity correction[16] to incorporate trials with zero events in one or both arms into the meta-analyses. The presence of heterogeneity was assessed using Cochran's Q test with a significance level of $P < 0.10$.[9] Heterogeneity was further quantified using I^2 statistics; we interpreted I^2 between 30% and 75% as moderate heterogeneity and >75% as serious heterogeneity.

Publication Bias

Funnel plots were used to assess the presence of small-study effects as an indication of publication bias. Harbord's test was used to statistically evaluate funnel plot asymmetry for dichotomous outcomes,[17] and Egger's test was used for continuous outcomes.[18] Statistical testing for asymmetry was not done for meta-analyses with less than 10 studies due to a lack of statistical power,[19] and visual inspection was performed instead.

Subgroup, Meta-regression, and Sensitivity Analyses

We conducted subgroup analyses based on the patient diagnosis at study inclusion (eg, septic shock vs. sepsis without shock). A subgroup analysis comparing different corticosteroid doses and duration was planned, but not conducted due to high heterogeneity in the regimens tested.

Additionally, a meta-regression analysis was conducted to assess the impact of mean patient age on the treatment effect for outcomes with ≥10 eligible studies, and post hoc sensitivity analyses were conducted excluding studies with high risks of bias to assess the impact of high-risk studies on our outcome measures.

Quality of Evidence

The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework.[20] A summary of study findings and the associated GRADE ratings are presented in a summary of findings table generated using GRADEpro GDT.[21]

RESULTS

The database search yielded 2851 results, of which 2291 were screened following deduplication. Thirty-one full texts from the title and abstract screening and 7 full texts from reference searching were retrieved, and 16 RCT publications (N = 973) were ultimately included in the systematic review.[22–37] The study selection process is illustrated in Figure 1, and citations for studies excluded during the full-text screening step are tabulated in Table,

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

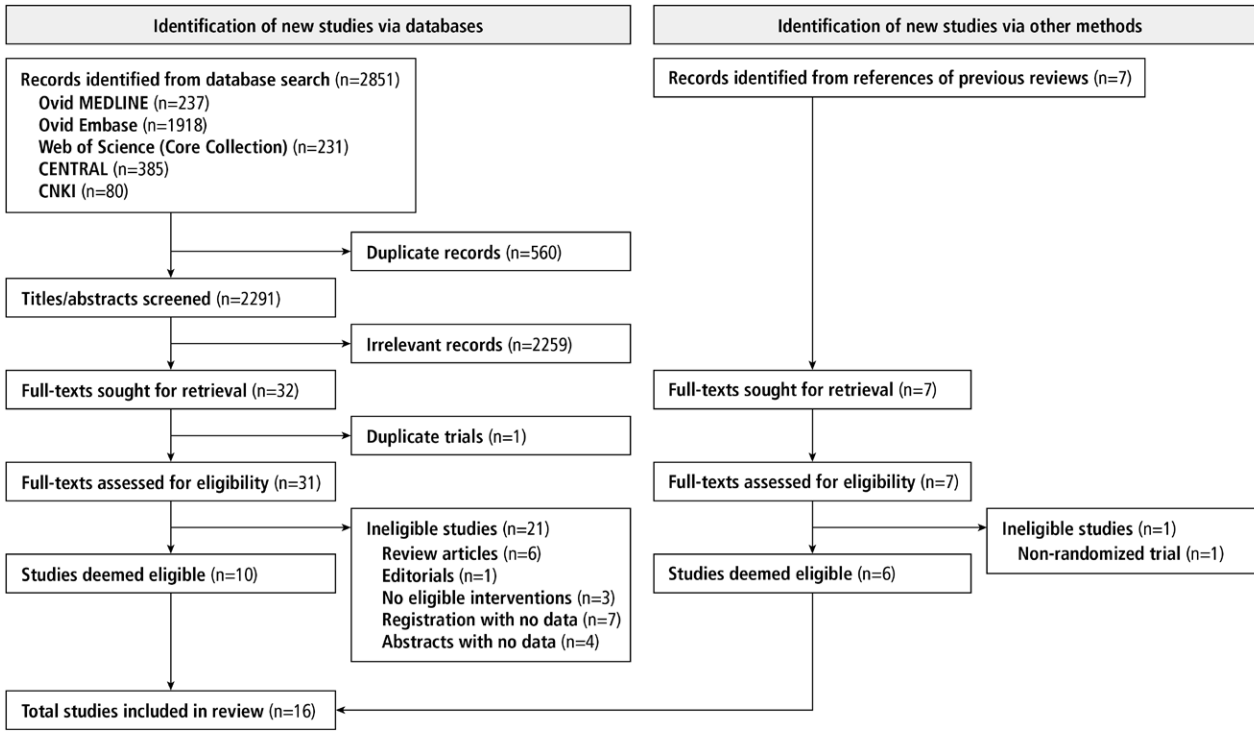
Identification of new studies via databases
Records identified from database search (n=2851)
Ovid MEDLINE (n=237)
Ovid Embase (n=1918)
Web of Science (Core Collection) (n=231)
CENTRAL (n=385)
CNKI (n=80)
Duplicate records (n=560)
Titles/abstracts screened (n=2291)
Irrelevant records (n=2259)
Full-texts sought for retrieval (n=32)
Duplicate trials (n=1)
Full-texts assessed for eligibility (n=31)
Ineligible studies (n=21)
Review articles (n=6)
Editorials (n=1)
No eligible interventions (n=3)
Registration with no data (n=7)
Abstracts with no data (n=4)
Studies deemed eligible (n=10)
Total studies included in review (n=16)
Identification of new studies via other methods
Records identified from references of previous reviews (n=7)
Full-texts sought for retrieval (n=7)
Full-texts assessed for eligibility (n=7)
Ineligible studies (n=1)
Non-randomized trial (n=1)
Studies deemed eligible (n=6)

FIGURE 1. PRISMA 2020 flowchart for the identification and selection of RCTs.

Supplemental Digital Content 8, http://links.lww.com/INF/F728. The characteristics of the included studies and patients are tabulated in Table, Supplemental Digital Content 9, http://links.lww.com/INF/F729.

Patient and Trial Characteristics

Among the included studies, 1 study[32] was quadruple-blinded, 5 studies[23,25,26,28,37] were double-blinded, and 2 studies[27,35] used open-label designs. The remaining studies did not report blinding methodologies. Only 2 studies[27,32] provided evidence of prospective trial registration.

The median number of patients randomized per trial was 54 (range 22–126), and the reported mean patient age ranged from 2.29 to 9 years old. Five trials (n = 306)[22–26] included patients with shock secondary to dengue hemorrhagic fever, 7 trials (n = 346)[31–37] included patients with septic shock without restrictions on the infectious source, 3 trials (n = 262)[28–30] included patients with sepsis or septic shock, and 1 trial (n = 59)[27] included patients with severe pneumonia with systemic inflammatory response syndrome without shock. Detailed definitions of sepsis and septic shock used by each study were tabulated in Table, Supplemental Digital Content 10, http://links.lww.com/INF/F730.

Intervention Characteristics

The corticosteroid regimens assessed were highly variable between studies. Four RCTs[22,25–27] used a single bolus of corticosteroids, with a dose ranging from 50 to 150 mg/kg equivalent of hydrocortisone.[38] Five RCTs[28,33,34,36,37] administered corticosteroids in multiple doses over a short duration of 24–48 hours, with daily dose ranging from 3 to 150 mg/kg equivalent of hydrocortisone. Four RCTs[23,29–31] administered corticosteroids over a long duration of 3–5 days (with or without additional days of tapering), with daily doses ranging from 10 to 50 mg/kg equivalent of hydrocortisone. Three RCTs[24,32,35] administered corticosteroids until stabilization/shock reversal, with daily doses ranging from 4 to 25 mg/kg equivalent of hydrocortisone.

Risk of Bias

A majority of included studies were rated as having a high risk of bias[22,24,29–31,33,34,36] or some concerns in regards to the risk of bias[23,25–28,35,37] (Fig. 2). Main concerns included unclear allocation concealment methods, unclear blinding methods and/or a lack of prospectively registered protocol or statistical analysis plan. Only 1 study[32] was evaluated to have a low risk of bias. Detailed RoB2 ratings for each included study are tabulated in Table, Supplemental Digital Content 11, http://links.lww.com/INF/F731.

Incidence of Mortality

The use of corticosteroids was associated with a lower risk of mortality compared to standard care and placebo (RR: 0.65, 95% CI: 0.50–0.85) based on 13 RCTs (N = 789),[22–29,31–33,35,37] with no heterogeneity ($I^2 = 0\%$, $P_Q = 0.56$) and no small-study effects (Harbord's test, $P = 0.37$, see Figure, Supplemental Digital Content 12, http://links.lww.com/INF/F732).

There were no significant differences between subgroups by diagnosis at study inclusion (test for subgroup difference, $P = 0.76$, Fig. 3). Meta-regression analysis by age showed no significant correlations ($P = 0.94$, see Figure, Supplemental Digital Content 13, http://links.lww.com/INF/F733). The sensitivity analysis excluding 5 high-risk-bias studies did not associate corticosteroid use with a lower risk of mortality (see Figure, Supplemental Digital Content 14, http://links.lww.com/INF/F734).

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

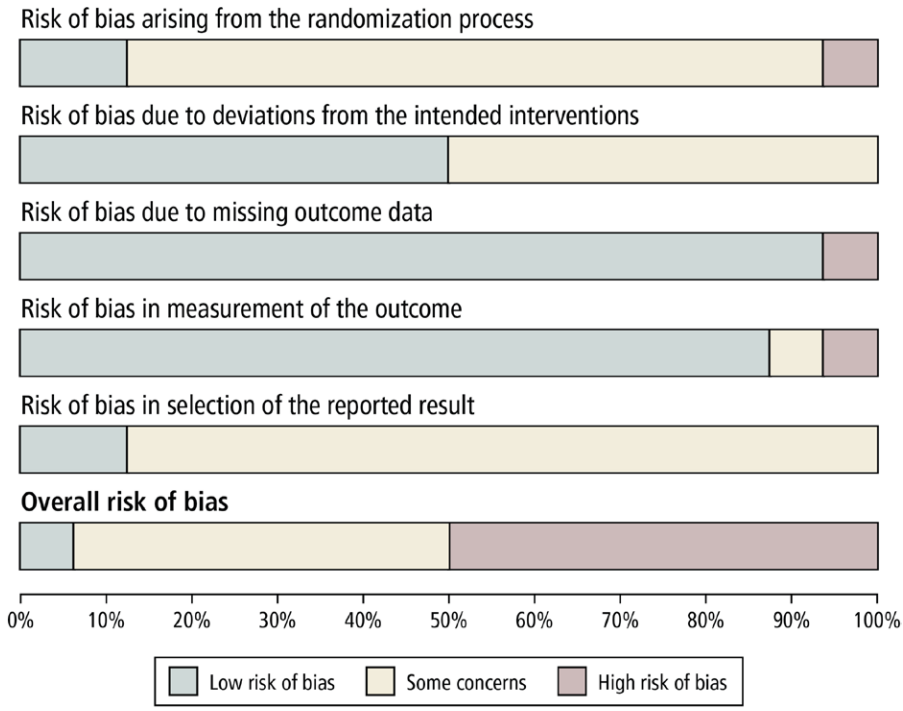

FIGURE 2. Bar plot showing the distribution of risk of bias ratings within each RoB2 domain.

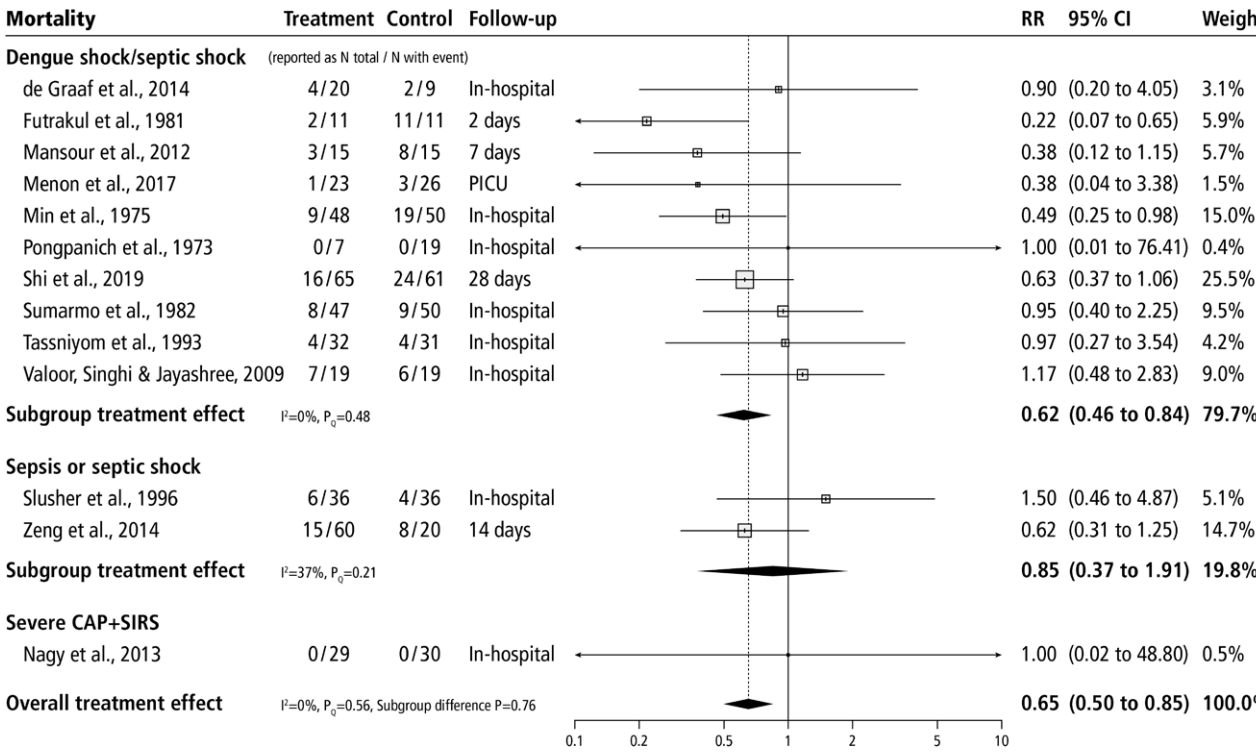
Mortality Treatment Control Follow-up RR 95% CI Weight
Dengue shock/septic shock (reported as N total / N with event)
de Graaf et al., 2014 4/20 2/9 In-hospital 0.90 (0.20 to 4.05) 3.1%
Futrakul et al., 1981 2/11 11/11 2 days 0.22 (0.07 to 0.65) 5.9%
Mansour et al., 2012 3/15 8/15 7 days 0.38 (0.12 to 1.15) 5.7%
Menon et al., 2017 1/23 3/26 PICU 0.38 (0.04 to 3.38) 1.5%
Min et al., 1975 9/48 19/50 In-hospital 0.49 (0.25 to 0.98) 15.0%
Pongpanich et al., 1973 0/7 0/19 In-hospital 1.00 (0.01 to 76.41) 0.4%
Shi et al., 2019 16/65 24/61 28 days 0.63 (0.37 to 1.06) 25.5%
Sumarmo et al., 1982 8/47 9/50 In-hospital 0.95 (0.40 to 2.25) 9.5%
Tassniyom et al., 1993 4/32 4/31 In-hospital 0.97 (0.27 to 3.54) 4.2%
Valoor, Singhi & Jayashree, 2009 7/19 6/19 In-hospital 1.17 (0.48 to 2.83) 9.0%
Subgroup treatment effect I²=0%, P_Q=0.48 0.62 (0.46 to 0.84) 79.7%
Sepsis or septic shock
Slusher et al., 1996 6/36 4/36 In-hospital 1.50 (0.46 to 4.87) 5.1%
Zeng et al., 2014 15/60 8/20 14 days 0.62 (0.31 to 1.25) 14.7%
Subgroup treatment effect I²=37%, P_Q=0.21 0.85 (0.37 to 1.91) 19.8%
Severe CAP+SIRS
Nagy et al., 2013 0/29 0/30 In-hospital 1.00 (0.02 to 48.80) 0.5%
Overall treatment effect I²=0%, P_Q=0.56, Subgroup difference P=0.76 0.65 (0.50 to 0.85) 100.0%
0.1
0.2
0.5
1
2
5
10

FIGURE 3. Forest plot illustrating the individual and pooled relative treatment effects from meta-analyses of RCTs for the outcome of mortality, stratified by patient diagnosis at study inclusion. RR <1 indicates beneficial treatment effects associated with corticosteroid regimens. CAP indicates community-acquired pneumonia; SIRS, systemic inflammatory response syndrome.

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Hospital Length of Stay

The use of corticosteroids was associated with lower hospital length of stay compared to standard care and placebo (MD: −3.76 days, 95% CI: −6.66 to −0.86 days) based on 5 RCTs (N = 322).[26,27,31,34,36] There was significant and serious heterogeneity (I^2 = 97%, $P_Q < 0.01$). Additionally, visual inspection of the funnel plot showed asymmetry, with smaller studies showing more beneficial treatment outcomes (see Figure, Supplemental Digital Content 15, http://links.lww.com/INF/F735).

There were no significant differences between subgroups by diagnosis at study inclusion ($P = 0.65$, Fig. 4A). The sensitivity analysis excluding 3 high-risk of bias studies did not demonstrate an association between corticosteroid use and reduced hospital length of stay (see Figure, Supplemental Digital Content 16, http://links.lww.com/INF/F736).

In addition to the studies included in the meta-analysis, 2 studies[28,32] reported nonparametric data that were deemed too skewed for mean imputation. Slusher et al[28] did not associate corticosteroid use with reduced hospital length of stay (Mann–Whitney *U* test $P = 0.59$). Menon et al[32] also found no associations between corticosteroid use and hospital length of stay (Cox Proportional-Hazards Regression $P = 0.79$).

PICU Length of Stay

The use of corticosteroids was associated with lower PICU length of stay compared to standard care and placebo (MD: −2.34 days, 95% CI: −3.14 to −1.53 days) based on 3 RCTs (N = 255)[29,31,32] with no heterogeneity (I^2 = 0%, P_Q = 0.47). Visual inspection of the funnel plot showed asymmetry, but the direction of asymmetry suggests that smaller studies showed less beneficial treatment outcomes (see Figure, Supplemental Digital Content 17, http://links.lww.com/INF/F737), which is contrary to what is expected with small-study effects. Thus, the funnel plot asymmetry is not indicative of publication bias for this outcome.

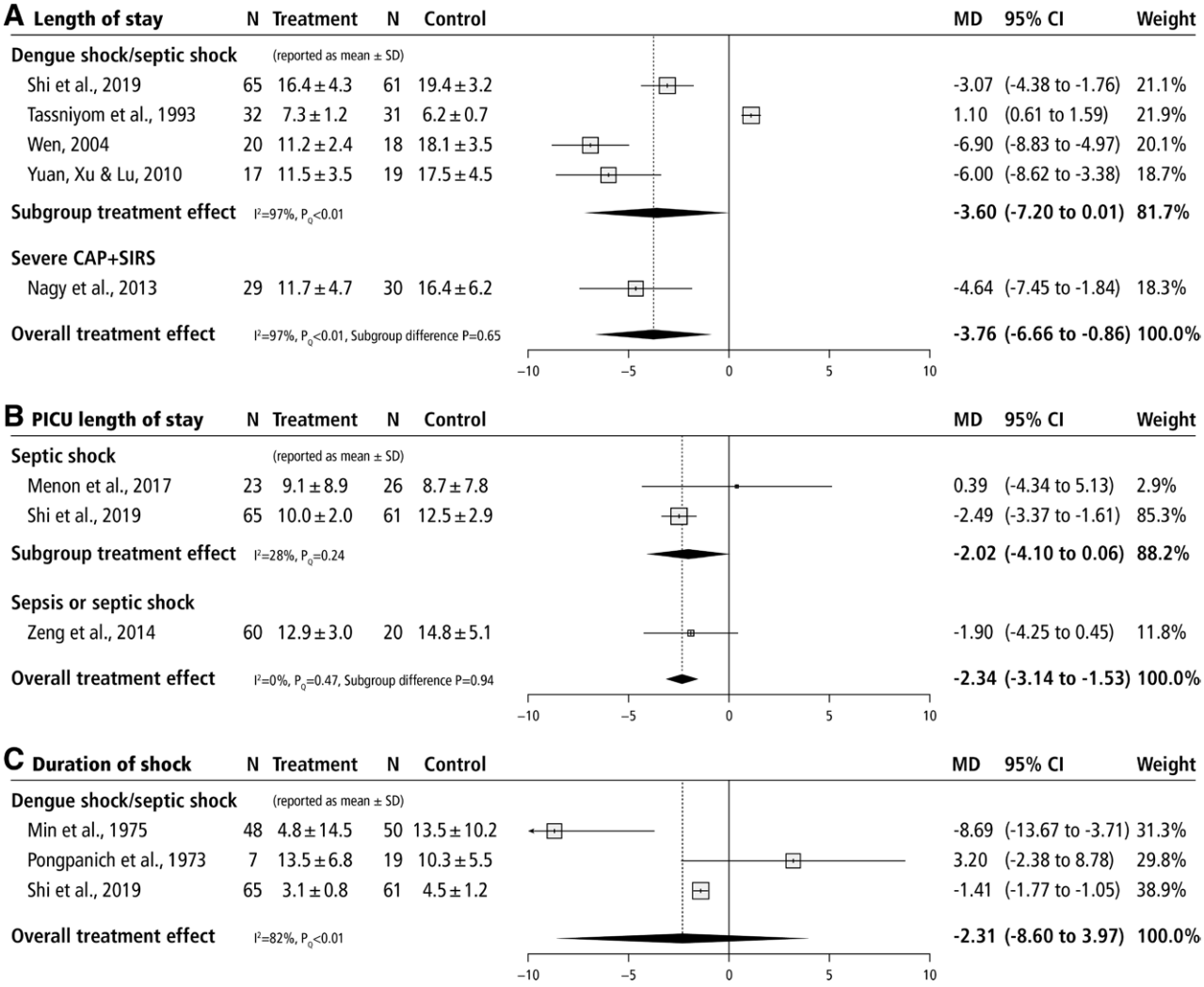
A Length of stay N Treatment N Control MD 95% CI Weight
Dengue shock/septic shock (reported as mean ± SD)
Shi et al., 2019 65 16.4 ± 4.3 61 19.4 ± 3.2 -3.07 (-4.38 to -1.76) 21.1%
Tassniyom et al., 1993 32 7.3 ± 1.2 31 6.2 ± 0.7 1.10 (0.61 to 1.59) 21.9%
Wen, 2004 20 11.2 ± 2.4 18 18.1 ± 3.5 -6.90 (-8.83 to -4.97) 20.1%
Yuan, Xu & Lu, 2010 17 11.5 ± 3.5 19 17.5 ± 4.5 -6.00 (-8.62 to -3.38) 18.7%
Subgroup treatment effect I²=97%, P_Q<0.01 -3.60 (-7.20 to 0.01) 81.7%
Severe CAP+SIRS
Nagy et al., 2013 29 11.7 ± 4.7 30 16.4 ± 6.2 -4.64 (-7.45 to -1.84) 18.3%
Overall treatment effect I²=97%, P_Q<0.01, Subgroup difference P=0.65 -3.76 (-6.66 to -0.86) 100.0%
−10 −5 0 5 10
B PICU length of stay N Treatment N Control MD 95% CI Weight
Septic shock (reported as mean ± SD)
Menon et al., 2017 23 9.1 ± 8.9 26 8.7 ± 7.8 0.39 (-4.34 to 5.13) 2.9%
Shi et al., 2019 65 10.0 ± 2.0 61 12.5 ± 2.9 -2.49 (-3.37 to -1.61) 85.3%
Subgroup treatment effect I²=28%, P_Q=0.24 -2.02 (-4.10 to 0.06) 88.2%
Sepsis or septic shock
Zeng et al., 2014 60 12.9 ± 3.0 20 14.8 ± 5.1 -1.90 (-4.25 to 0.45) 11.8%
Overall treatment effect I²=0%, P_Q=0.47, Subgroup difference P=0.94 -2.34 (-3.14 to -1.53) 100.0%
−10 −5 0 5 10
C Duration of shock N Treatment N Control MD 95% CI Weight
Dengue shock/septic shock (reported as mean ± SD)
Min et al., 1975 48 4.8 ± 14.5 50 13.5 ± 10.2 -8.69 (-13.67 to -3.71) 31.3%
Pongpanich et al., 1973 7 13.5 ± 6.8 19 10.3 ± 5.5 3.20 (-2.38 to 8.78) 29.8%
Shi et al., 2019 65 3.1 ± 0.8 61 4.5 ± 1.2 -1.41 (-1.77 to -1.05) 38.9%
Overall treatment effect I²=82%, P_Q<0.01 -2.31 (-8.60 to 3.97) 100.0%
−10 −5 0 5 10

FIGURE 4. Forest plot illustrating the individual and pooled relative treatment effects from meta-analysis of RCTs for the outcome of hospital length of stay, PICU length of stay and duration of shock, stratified by patient diagnosis at study inclusion. An MD <0 indicates beneficial treatment effects associated with corticosteroid regimens. A: Meta-analysis for the outcome of hospital length of stay. B: Meta-analysis for the outcome of PICU length of stay. C: Meta-analysis for the outcome of shock duration. CAP indicates community-acquired pneumonia; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

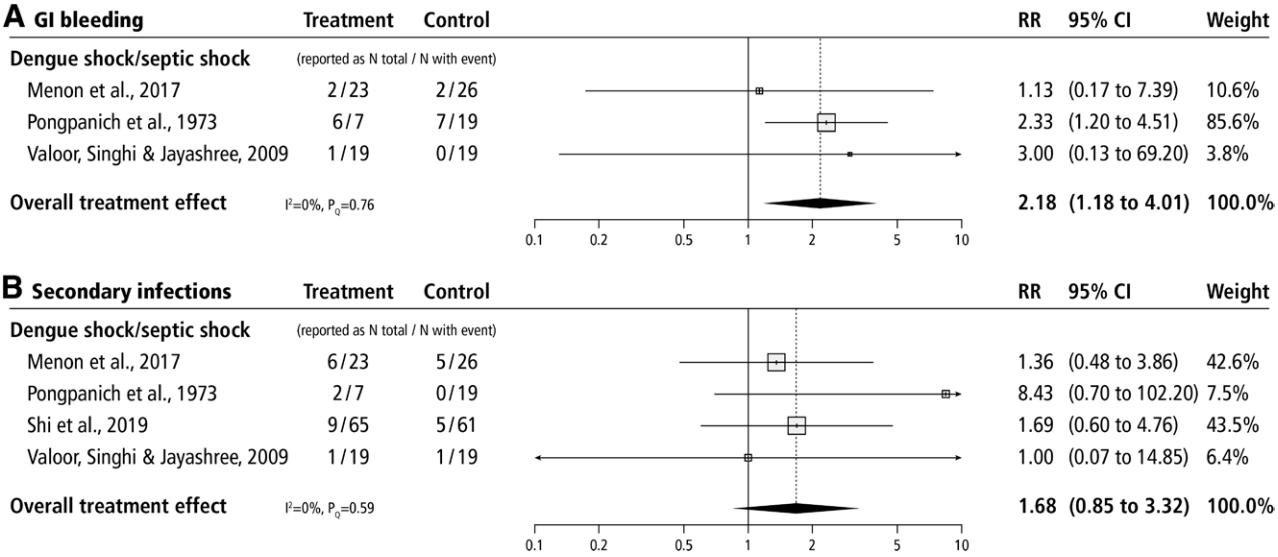
A GI bleeding
Treatment
Control
RR
95% CI
Weight
Dengue shock/septic shock
(reported as N total / N with event)
Menon et al., 2017 2/23 2/26 1.13 (0.17 to 7.39) 10.6%
Pongpanich et al., 1973 6/7 7/19 2.33 (1.20 to 4.51) 85.6%
Valoor, Singhi & Jayashree, 2009 1/19 0/19 3.00 (0.13 to 69.20) 3.8%
Overall treatment effect I²=0%, P_Q=0.76 2.18 (1.18 to 4.01) 100.0%
0.1 0.2 0.5 1 2 5 10
B Secondary infections
Treatment
Control
RR
95% CI
Weight
Dengue shock/septic shock
(reported as N total / N with event)
Menon et al., 2017 6/23 5/26 1.36 (0.48 to 3.86) 42.6%
Pongpanich et al., 1973 2/7 0/19 8.43 (0.70 to 102.20) 7.5%
Shi et al., 2019 9/65 5/61 1.69 (0.60 to 4.76) 43.5%
Valoor, Singhi & Jayashree, 2009 1/19 1/19 1.00 (0.07 to 14.85) 6.4%
Overall treatment effect I²=0%, P_Q=0.59 1.68 (0.85 to 3.32) 100.0%
0.1 0.2 0.5 1 2 5 10

FIGURE 5. Forest plot illustrating the individual and pooled relative treatment effects from meta-analysis of RCTs for safety outcomes, stratified by patient diagnosis at study inclusion. An RR >1 indicates harmful treatment effects associated with corticosteroid regimens. A: Meta-analysis for the outcome of gastrointestinal bleeding. B: Meta-analysis for the outcome of secondary infections. GI indicates gastrointestinal.

Subgroup analysis by diagnosis at study inclusion showed no statistically significant difference between subgroups (test for subgroup difference, $P = 0.94$, Fig. 4B). Only 1 study, by Menon et al,[32] remained after excluding 2 high-risk of bias studies. The study did not find an association between the use of corticosteroids and PICU length of stay.

Duration of Shock

The use of corticosteroids was not associated with changes in duration of shock compared to standard care and placebo (MD: −2.31 hours, 95% CI: −8.60 to 3.97 hours) based on 3 RCTs (N = 250).[23,24,31] There was significant and serious heterogeneity (I^2 = 82%, $P_Q < 0.01$). There was no notable asymmetry on visual inspection of the funnel plot (see Figure, Supplemental Digital Content 18, http://links.lww.com/INF/F738).

Only 1 RCT publication, by Min et al,[23] remained after excluding 2 high-risk of bias studies. The study reported a lower duration of shock among patients receiving a 3-day course of adjuvant hydrocortisone (Fig. 4C).

Safety Outcomes

Two studies reported the incidence of adverse events, but they were not pooled as the category of events assessed differed substantially. The study by Wang et al[30] assessed the incidence of heart palpitations, constipation and pruritus and did not find an association between the use of corticosteroids and increased risk of these events (χ^2 test $P > 0.05$). The study by Nagy et al[27] assessed the incidence of pleural effusions, empyema and abscess formation. The use of corticosteroid was associated with a lower risk of these events compared to placebo (χ^2 test $P < 0.05$). No study reported any serious adverse events.

In terms of corticosteroid-specific adverse events, the use of corticosteroids was associated with a higher risk of gastrointestinal bleeding compared to standard care and placebo (RR: 2.18, 95% CI: 1.18–4.01, Fig. 5A) based on 3 RCTs (N = 113),[24,32,35] with no heterogeneity ($I^2 = 0\%$, $P_Q = 0.76$). The use of corticosteroids was not associated with the risk of secondary infections compared to standard care and placebo (RR: 1.68, 95% CI: 0.85–3.32, Fig. 5B) based on 4 RCTs (N = 239),[24,31,32,35] with no heterogeneity (I^2 = 0%, $P_Q = 0.59$). No asymmetry was observed for both outcomes on visual inspection of the funnel plots (see Figures, Supplemental Digital Content 19 and 20, http://links.lww.com/INF/F739). In the sensitivity analysis excluding high risk of bias studies for the outcome of gastrointestinal bleeding, the use of corticosteroids was not associated with increased risk of gastrointestinal bleeding (see Figures, Supplemental Digital Content 21 and 22, http://links.lww.com/INF/F740).

Only 1 study, by Menon et al,[32] assessed and reported the incidence of hyperglycemia (defined as requirement for insulin infusion). The use of corticosteroids was not associated with an increased risk of hyperglycemia (Fisher exact test, $P = 0.17$). No study assessed the incidence of hypernatremia.

Quality of Evidence

A summary of review findings and the associated GRADE quality of evidence ratings are reported in Table 1.

DISCUSSION

Main Findings

This systematic review and meta-analysis, which included 16 trials with 973 pediatric patients diagnosed with sepsis and septic shock, found that corticosteroids may be associated with a 35% lower risk of mortality. It may also be associated with a 4-day shorter mean hospital length of stay, and a 2-day shorter mean PICU length of stay, compared to standard care and placebo, but the evidence is very uncertain according to GRADE. Corticosteroid use may be associated with a 2-fold higher risk of gastrointestinal bleeding versus standard care and placebo, but the evidence is very uncertain according to GRADE. These findings support further investigations into the use of corticosteroids and highlight the need to focus on assessments of corticosteroid-related adverse events; however, they are insufficient for supporting routine clinical use of corticosteroids for pediatric sepsis and septic shock.

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 1. GRADE Summary of Findings Table

Outcomes	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)*			N Patients (N studies)	Quality of Evidence (GRADE)
		Risk Without Corticosteroids	Risk With Corticosteroids	Risk Difference (95% CI)		
Incidence of mortality	**RR 0.65** (0.50–0.85)	260 per 1000	**169 per 1000** (130–221)	**91 fewer per 1000** (130 fewer to 39 fewer)	789 (13)	⨁⨁◯◯ Low¶
Hospital length of stay†	-	The mean hospital length of stay was 15.77 days	The anticipated mean hospital length of stay is **12.01 days** (9.11–14.91)	**MD 3.76 fewer days** (6.66 fewer to 0.86 fewer)	322 (5)	⨁◯◯◯ Very low¶‖**††
PICU length of stay‡	-	The mean PICU length of stay was 12.01 days	The anticipated mean PICU length of stay is **9.67 days** (8.87–10.48)	**MD 2.34 fewer days** (3.14 fewer to 1.53 fewer)	255 (3)	⨁◯◯◯ Very low¶††
Duration of shock§	-	The mean duration of shock was 8.81 days	The anticipated mean duration of shock is **6.50 days** (0.21–12.78)	**MD 2.31 fewer days** (8.60 fewer to 3.97 more)	250 (3)	⨁◯◯◯ Very low¶‡‡
Incidence of gastrointestinal bleeding	**RR 2.18** (1.18–4.01)	141 per 1000	**307 per 1000** (166–564)	**166 more per 1000** (25 more to 423 more)	113 (3)	⨁◯◯◯ Very low¶§§
Incidence of secondary infections	**RR 1.68** (0.85–3.32)	88 per 1000	**148 per 1000** (75–292)	**60 more per 1000** (13 fewer to 204 more)	239 (4)	⨁◯◯◯ Very low¶¶¶

*The absolute risk in the intervention group (and its 95% confidence interval) is based on the baseline risk in the control group and the relative effect of the intervention (and its 95% CI). The baseline risk in the control group is calculated using GRADEpro GDT, by dividing the total control group sample size by the total incidence in the control group.

†An arbitrary clinically important margin of 24 hours (1 day) was used for the OIS calculation for hospital length of stay. The final OIS used for imprecision assessment was 225 patients per arm.

‡An arbitrary clinically important margin of 24 hours (1 day) was used for the OIS calculation for PICU length of stay. The final OIS used for imprecision assessment was 320 patients per arm.

§An arbitrary clinically important margin of 24 hours (1 day) was used for the OIS calculation for duration of shock. The final OIS used for imprecision assessment was 1026 patients per arm.

¶Downgraded by 2 levels due to limitations in the study design or execution (risk of bias). A majority of analyzed studies were rated as having high risk or some concerns regarding risk of bias, and the pooled effect was sensitive to the removal of high risk of bias studies.

‖Downgraded by 2 levels due to serious inconsistency of results. I^2 statistics indicate the possible presence of serious heterogeneity.

**While visual inspection of the funnel plot showed patterns indicative of small study effects, the small number of data points and the lack of quantitative assessment make it difficult to ascertain whether publication bias exists. Thus, this outcome was not downgraded based on assessment of publication biases.

††Downgraded by 1 level due to imprecision. The sample size analyzed for this outcome is substantially lower than the calculated OIS for the outcome.

‡‡Downgraded by 2 levels due to imprecision. The sample size analyzed for this outcome is substantially lower than the calculated OIS for the outcome, and the CI of the outcome measure crosses the line of null effect.

§§Downgraded by 1 level due to imprecision. The ratio of the upper and lower bounds of the CI is >3 for this dichotomous outcome, which used RR as the treatment effect.

¶¶Downgraded by 2 levels due to imprecision. The ratio of the upper and lower bounds of the CI is >3 for this dichotomous outcome, which used RR as the treatment effect. The CI of the outcome measure also crosses the line of null effect.

OIS indicates optimal information size.

GRADE Working Group quality of evidence rating[20]

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

A Continued Lack of Pediatric Sepsis Trials

Compared to the 2013 review by Menon et al,[7] the additional 8 RCTs identified in the current review highlight ongoing efforts to fill the gaps in current pediatric sepsis research regarding corticosteroid use, yet they also underscore the need for more extensive research given their small scale and inherent variability in patient populations and interventions. Previous research cites difficulty with recruitment due to parental apprehension toward research procedures, dropouts after randomization due to strong preferences toward treatment arms and a lack of staffing and resources, as key barriers toward conducting large-scale pediatric RCTs.[39,40] The decline of pediatric mortality from sepsis in high-income countries,[4] where more funding for large trials is typically available, compounds these issues. Strategies such as designing partially randomized patient-preference trials,[41] using programmed eligibility alerts in electronic medical record systems, and deferred consent in cases of absent decision-makers,[42] may be potential strategies for improving the viability of large pediatric sepsis trials.

How Can Corticosteroid Use be Optimized?

While the current review associated the use of corticosteroids with beneficial effects in pediatric sepsis patients, the question of how to best optimize the use of corticosteroids—for instance, choosing the optimal dose, timing and duration, or choosing candidates who benefit the most from corticosteroids—remains unanswered. Recent research has described distinct transcriptomics- and biomarker-based subphenotypes of sepsis in adult patients with distinct illness characteristics and trajectories, and it has been postulated that differences in subphenotypes could affect patient response to sepsis treatment.[43] These subphenotypes may apply to the pediatric population as well.[44] Thus, it is crucial for future pediatric sepsis trials to stratify patient enrollment based on sepsis subphenotypes, which can help in identifying specific patient clusters that benefit the most from corticosteroid interventions. Upcoming pediatric sepsis trials such as SHIPSS (Stress Hydrocortisone In Pediatric Septic Shock)[45] and PRECISE (Personalized Immunomodulation in Pediatric Sepsis-induced MODS)[46,47] are already adopting these phenotyping techniques.

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

A Need to Focus on Safety Outcomes

In this review, we aimed to study adverse events that have been commonly observed in critically ill patients receiving corticosteroids.[48] We found that current RCTs focused on efficacy outcomes and did not often assess or report the safety of corticosteroids in this population. Even when studies reported safety outcomes, the investigators assessed very different categories of adverse events with no standardization of event definitions and severity gradings. Future investigations should adhere to established guidelines such as CONSORT Harms[49] when reporting safety data, which can help produce evidence that allows clinicians to better balance the risks and benefits associated with corticosteroid use in pediatric patients with sepsis.

Study Strengths and Limitations

This systematic review was prospectively registered on PROSPERO, followed PRISMA guidelines, utilized GRADE quality of evidence assessments, and included extensive a priori subgroup analyses based on underlying diagnoses and risk of bias to decrease heterogeneity and improve clinical applicability. However, despite the inclusion of additional studies, many included trials still had high risks of bias and enrolled limited numbers of patients. These trials also had considerable variability in demographics and the studied corticosteroid interventions, which limited the certainty of findings. Additional trials are needed to improve the confidence of these findings and provide additional insights into appropriate patient selection and corticosteroid regimens.

CONCLUSIONS

In a systematic review and meta-analysis of 16 RCTs, corticosteroids may be associated with a lower risk of mortality and decreased hospital and PICU length of stay, compared to standard care and placebo. At the same time, corticosteroid use may be associated with a higher risk of gastrointestinal bleeding versus standard care and placebo. These findings suggest that corticosteroids may improve outcomes among this population; however, these findings are based on low to very low-quality of evidence, and the beneficial effects of corticosteroids must be weighed carefully against the risk of adverse events. Additional trials are required to improve the confidence of these findings and to provide additional insights into appropriate patient selection and corticosteroid regimens.

REFERENCES

1. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med*. 2020;21:e52–e106.
2. Cecconi M, Evans L, Levy M, et al. Sepsis and septic shock. *Lancet*. 2018;392:75–87.
3. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395:200–211.
4. Tan B, Wong JJ-M, Sultana R, et al. Global case-fatality rates in pediatric severe sepsis and septic shock: a systematic review and meta-analysis. *JAMA Pediatr*. 2019;173:352–362.
5. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358:111–124.
6. Venkatesh B, Finfer S, Cohen J, et al; ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med*. 2018;378:797–808.
7. Menon K, McNally D, Choong K, et al. A systematic review and meta-analysis on the effect of steroids in pediatric shock. *Pediatr Crit Care Med*. 2013;14:474–480.
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *PLoS Med*. 2021;18:e1003583.
9. *Cochrane Handbook for Systematic Reviews of Interventions (v6.2)*. The Cochrane Collaboration; 2021.
10. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for treating sepsis in children and adults. *Cochrane Database Syst Rev*. 2019;12:CD002243.
11. Shi J, Luo D, Wan X, et al. Detecting the skewness of data from the five-number summary and its application in meta-analysis. *Stat Methods Med Res*. 2023;32:1338–1360.
12. Shi J, Luo D, Weng H, et al. Optimally estimating the sample standard deviation from the five-number summary. *Res Synth Methods*. 2020;11:641–654.
13. Luo D, Wan X, Liu J, et al. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27:1785–1805.
14. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
15. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
16. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23:1351–1375.
17. Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006;25:3443–3457.
18. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
19. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
20. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926.
21. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383–394.
22. Futrakul P, Vasanauthana S, Poshyachinda M, et al. Pulse therapy in severe form of dengue shock syndrome. *J Med Assoc Thai*. 1981;64:485–491.
23. Min M, U T, Aye M, et al. Hydrocortisone in the management of dengue shock syndrome. *Southeast Asian J Trop Med Public Health*. 1975;6:573–579.
24. Pongpanich B, Bhanchet P, Phanichyakarn P, et al. Studies on dengue hemorrhagic fever. Clinical study: an evaluation of steroids as a treatment. *J Med Assoc Thai*. 1973;56:6–14.
25. Sumarmo D, Talogo W, Asrin A, et al. Failure of hydrocortisone to affect outcome in dengue shock syndrome. *Pediatrics*. 1982;69:45–49.
26. Tassniyom S, Vasanawathana S, Chirawatkul A, et al. Failure of high-dose methylprednisolone in established dengue shock syndrome: a placebo-controlled, double-blind study. *Pediatrics*. 1993;92:111–115.
27. Nagy B, Gaspar I, Papp A, et al. Efficacy of methylprednisolone in children with severe community acquired pneumonia. *Pediatr Pulmonol*. 2013;48:168–175.
28. Slusher T, Gbadero D, Howard C, et al. Randomized, placebo-controlled, double blinded trial of dexamethasone in African children with sepsis. *Pediatr Infect Dis J*. 1996;15:579–583.
29. Zeng R. [The clinical effects comparison of different doses of methylprednisolone in the treatment of children with severe sepsis]. *J Chengdu Med Coll*. 2014;9:734–737.
30. Wang QZ, Lin XF, Zhu HL. [Influences of Dexamethasone combined with cefoperazone and sulbactam on efficacy of sepsis in children and serum PCT, Presepsin and NT-proBNP]. *Drug Eval Res*. 2022;45:118–123.
31. Shi XN, Xu MX, Geng WJ, et al. [Therapeutic effects of early application of low-dose glucocorticoid on septic shock in children and its effects on immune function of patients]. *Hebei Med J*. 2019;41:1770–1774.

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

32. Menon K, McNally D, O'Hearn K, et al; Canadian Critical Care Trials Group. A randomized controlled trial of corticosteroids in pediatric septic shock: a pilot feasibility study. *Pediatr Crit Care Med*. 2017;18:505–512.
33. de Graaf H, Ramakrishnan KA, Pappachan J, et al. Abstract 621: evaluation of corticosteroid replacement therapy in children with severe septic shock – a randomised intervention trial. *Pediatr Crit Care Med*. 2014;15:141.
34. Wen WY. [Observation on the treatment of septic shock in children with high-dose methylprednisolone]. *J Pract Diagn Ther*. 2004;18:404–405.
35. Valoor HT, Singhi S, Jayashree M. Low-dose hydrocortisone in pediatric septic shock: an exploratory study in a third world setting. *Pediatr Crit Care Med*. 2009;10:121–125.
36. Yuan YH, Xu ZY, Lu XL. [Observation on the efficacy of hydrocortisone in the treatment of septic shock in children]. *Chin J Misdiagn*. 2010;10:61.
37. Mansour M, Tarek M, Zayton Y, et al. 1576 effect of dexamethasone therapy on the expression of macrophage migration inhibitory factor in critically ill children with septic shock. *Arch Dis Child*. 2012;97:A446–A446.
38. Singer M, Webb A: *Oxford Handbook of Critical Care, 3rd Ed*. Oxford, United Kingdom: Oxford University Press; 2009.
39. Beasant L, Brigden A, Parslow RM, et al. Treatment preference and recruitment to pediatric RCTs: a systematic review. *Contemp Clin Trials Commun*. 2019;14:100335.
40. Watson SE, Smith P, Snowden J, et al. Facilitators and barriers to pediatric clinical trial recruitment and retention in rural and community settings: a scoping review of the literature. *Clin Transl Sci*. 2022;15:838–853.
41. Wasmann KA, Wijsman P, van Dieren S, et al. Partially randomised patient preference trials as an alternative design to randomised controlled trials: systematic review and meta-analyses. *BMJ Open*. 2019;9:e031151.
42. McBain KL, Payne ET, Sharma R, et al. Strategies to maximize enrollment in a prospective study of comatose children in the PICU. *Pediatr Crit Care Med*. 2016;17:246–250.
43. Komorowski M, Green A, Tatham KC, et al. Sepsis biomarkers and diagnostic tools with a focus on machine learning. *EBioMedicine*. 2022;86:104394.
44. Weiss SL, Fitzgerald JC. Pediatric sepsis diagnosis, management, and sub-phenotypes. *Pediatrics*. 2024;153:e2023062967. Available at: http://dx.doi.org/10.1542/peds.2023-062967.
45. Stress Hydrocortisone In Pediatric Septic Shock. *ClinicalTrials.gov* [cited 2024 Jun 9]. Available at: https://clinicaltrials.gov/ct2/show/NCT03401398. Accessed May 1, 2024.
46. GM-CSF for Reversal of Immunoparalysis in Pediatric Sepsis-induced MODS. *ClinicalTrials.gov* [cited 2024 Jun 9]. Available at: https://clinicaltrials.gov/ct2/show/NCT05266001. Accessed May 1, 2024.
47. Targeted Reversal of Inflammation in Pediatric Sepsis-induced MODS. [cited 2024 Jun 9] Available at: https://clinicaltrials.gov/ct2/show/NCT05267821. Accessed May 1, 2024.
48. Young A, Marsh S. Steroid use in critical care. *BJA Educ*. 2018;18:129–134.
49. Junqueira DR, Zorzela L, Golder S, et al; CONSORT Harms Group. CONSORT Harms 2022 statement, explanation, and elaboration: updated guideline for the reporting of harms in randomised trials. *BMJ*. 2023;381:e073725.

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.